Drug Design in Protozoa

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Trypanosomatidae (*Trypanosoma, Leishmania*) are the causative agents of important diseases of man, such as sleeping sickness in tropical Africa, Chagas' disease in Latin America and the leishmaniases in all tropical and sub-tropical parts of the world. All members of the trypanosomatid family have the first part of the glycolytic pathway sequestered inside a microbody-like organelle called the glycosome, rather than in the cytosol, as is the case in other organisms. Moreover, the African trypanosome is entirely dependent on glycolysis for ATP synthesis, due to the lack of a functional mitochondrion. For the above reasons the glycolytic enzymes of trypanosomes are considered suitable targets for the rational design of new anti-trypanosomal drugs. Two approaches aimed at the inhibition of the glycolytic enzymes have been followed.

(i) Most glycosomal enzymes are characterized by the presence on their surface of patches of positively charged amino acids: the so-called positive hotspots. A series of compounds have been synthesized that bind to the hotspots of these glycosomal proteins and so behave as specific and selective inhibitors of trypanosome glycolysis.

(ii) The crystal structures of both the trypanosome and the human NAD: glyceraldehyde-3-phosphate dehydrogenase complexes have been solved. Comparison of the two structures revealed interesting differences at the level of the NAD-binding pocket near the cofactor's adenine ring. Starting from adenosine (a weak inhibitor that inhibits both enzymes equally well, Ki=30 mM) as reference compound, analogues were synthesized that exploited two hydrophobic pockets in the adenosine-binding cavity, specific to the trypanosome enzyme. This led to the synthesis of a compound that gave an improved inhibition of the parasite enzyme by 167-fold when compared with adenosine. The selectivity with respect to the mammalian enzyme was improved by a factor of 500.

Source: https://www.industrydocuments.ucsf.edu/docs/mgmv0000